

Procedure for Rush and Cluster Immunotherapy

This Instant Reference is based upon current clinical practice and extensive review of the literature and has been developed by the Joint Task Force on Practice Parameters of the American College of Allergy, Asthma & Immunology (ACAAI), the American Academy of Allergy, Asthma and Immunology (AAAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI).

Rush and Cluster Immunotherapy represent accelerated schedules of immunotherapy. They are designed to allow a patient to reach a maintenance dose in a shorter time than the more traditional weekly immunotherapy. Though this may provide improved convenience, it also is associated with an increased risk of allergic reactions.

Accelerated Immunotherapy schedules

There are a number of advantages and disadvantages to using an accelerated immunotherapy schedule:

Advantages

- May be more convenient if the duration of weekly visits is shortened
- Improved adherence
- Clinical benefit may occur more rapidly
- May be safer because the number of vials being used is reduced once a maintenance dose is reached

Disadvantages

- There is an increased risk of systemic reactions during the procedure
- Increased time and resources are needed in the health facility to give multiple injections

Indications for accelerated schedules

While there are no firm indications for accelerated schedules, the following patients and/or situations may benefit from such schedules:

- Patients who have not been able to reach a maintenance dose on weekly immunotherapy due to systemic reactions or due to sub adherence
- Patients whose schedule precludes weekly injections for a prolonged time
- Patients with asthma that cannot be adequately controlled but who can be controlled long enough to reach a maintenance dose with an accelerated schedule

Consent for accelerated schedules

When an accelerated schedule is used then additional informed consent should be obtained in which the additional procedures, risks and benefits are disclosed. This may be obtained using a separate consent form designed for accelerated immunotherapy in addition to a form designed for weekly immunotherapy.

Premedication

Premedication is given in an attempt to reduce the risk and severity of a systemic reaction during the procedure.

Factors that increase the risk of a systemic reaction include:

- Poorly-controlled asthma
- Extremely high sensitivity to the allergens
- Poor suppression of skin reactivity with premedication

Cluster Immunotherapy

It may be desirable to have the patient take an H1 and H2 antagonist on the day that they will receive cluster injections, however, there is no evidence that doing so reduces the likelihood or severity of a local or systemic reaction.

Rush Immunotherapy (RIT)

Patients should receive prophylaxis starting 2 days prior to the procedure to reduce the likelihood of a systemic reaction.

<i>H-1 antagonist</i>	<ul style="list-style-type: none"> • Cetirizine • Diphenhydramine
<i>H-2 antagonist</i>	<ul style="list-style-type: none"> • Ranitidine
<i>Corticosteroid</i>	<ul style="list-style-type: none"> • Prednisone
<i>Leukotriene receptor antagonist</i>	<ul style="list-style-type: none"> • Montelukast

Schedules for administration of accelerated IT

Cluster Immunotherapy (example)

Visit Number	Volume (mL)	Dilution (v/v)	Vial Color	Dose (mg)	Cum Dose (mg)
1	0.10	1:1000	green	0.1	0.1
	0.40	1:1000	green	0.4	0.5
	0.10	1:100	blue	1.0	1.5
2	0.20	1:100	blue	2.0	3.5
	0.40	1:100	blue	4.0	7.5
	0.07	1:10	yellow	7.0	14.5
3	0.10	1:10	yellow	10.0	24.5
	0.15	1:10	yellow	15.0	39.5
	0.25	1:10	yellow	25.0	64.5
4	0.35	1:10	yellow	35.0	99.5
	0.50	1:10	yellow	50.0	149.5
	0.07	1:1	red	70.0	219.5
5	0.10	1:1	red	100.0	319.5
	0.15	1:1	red	150.0	469.5
	0.20	1:1	red	200.0	669.5
6	0.30	1:1	red	300.0	969.5
	0.40	1:1	red	400.0	1,369.5
	0.50	1:1	red	500.0	1,869.5

Rush Immunotherapy (1-day schedule)

Time (minutes)	Volume (mL)	Dilution (v/v)	Vial Color	Dose (mg)	Cum Dose (mg)
0:00	0.30	1:1000	green	0.3	0.3
0:30	0.10	1:100	blue	1.0	1.3
1:00	0.30	1:100	blue	3.0	4.3
1:30	0.05	1:10	yellow	5.0	9.3
2:00	0.15	1:10	yellow	15.0	24.3
3:00	0.30	1:10	yellow	30.0	54.3
4:00	0.05	1:1	red	50.0	104.3
5:00	0.10	1:1	red	100.0	204.3
6:00	0.20	1:1	red	200.0	404.3

This should be followed by 8 weekly injections building up to and at the maintenance dose. The frequency can then be reduced to every 2 weeks.

Instant Reference for Rush and Cluster Immunotherapy *continued*

Other points

Rush Immunotherapy

- An IV with a heparin lock often is inserted as a precaution prior to the procedure.
- It may be necessary to stop giving injections if the patient develops a large local reaction or evidence of a systemic reaction.
- For extremely sensitive individuals it may be desirable to stop giving injections after the 1:10 (v/v) vial to avoid inducing a systemic reaction.
- Patients should be observed for at least 2 hours after the last injection during the rush day.

Billing for accelerated immunotherapy

- It is best to obtain prior authorization if possible
- An appropriate CPT code to use is 95180 which is billed on an hourly basis. This should be billed for the pre-approved amount.

Cluster Immunotherapy

Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules.

Cluster schedules are designed to accelerate the buildup phase of immunotherapy. Cluster immunotherapy usually is characterized by visits for administration of allergen immunotherapy extract 1 or 2 times per week with a schedule that contains fewer total injections than are used with conventional immunotherapy. With cluster immunotherapy, 2 or more injections are given per visit on nonconsecutive days. The injections are typically given at 30-minute intervals, but longer intervals have also been used in some protocols. This schedule can permit a patient to reach a maintenance dose in as brief a period of time as 4 weeks. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules. The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.

Rush Immunotherapy

Summary Statement 48: Rush schedules can be used to reach a maintenance dose more quickly than weekly schedules.

Rush schedules are more rapid than cluster immunotherapy. An early study used a schedule that permitted patients to achieve a maintenance dose in 6 days; however, patients were required to remain in the hospital.²⁶⁸ As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly. The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections

over the course of 4 hours. Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours. The advantage of a cluster or rush schedule is that it permits patients to attain a therapeutically effective maintenance dose more rapidly than with a conventional schedule. Controlled studies have shown symptomatic improvement shortly after reaching maintenance doses by using cluster and rush schedules.

Systemic Reactions

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions.

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study. Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing. Systemic reactions with rush schedules have been reported to occur up to 2 hours after the final injection. For that reason, individuals receiving rush immunotherapy should remain under physician supervision for a longer waiting period than the usual 30 minutes recommended for conventional schedules (eg, 1.5-3 hours on the day of allergen immunotherapy extract administration). Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.

Premedication Prophylaxis

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions.

Premedication with a nonsedating antihistamine (loratadine) 2 hours before the first injection of each visit reduced both the number and severity of systemic reactions during cluster immunotherapy. Premedication with a 3-day course of prednisone, an H1 histamine receptor antagonist, and an H2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.²⁷² In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group. There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies.

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The publication of this Instant Reference for Health Professionals

For the complete Immunotherapy practice parameter, see J Allergy Clin Immunol, 2007. 120(3 Suppl): p. S25-85